This listing of claims will replace all prior versions, and listings, of claims in the application

LISTING OF CLAIMS

1. (currently amended) A non-human mutant mammal, deficient in an endogenous Sigma receptor, whose genome comprises ~~contains~~ a mutation comprising a disruption in a gene of an endogenous Sigma receptor, wherein said gene disruption gives rise to a non-human mutant mammal lacking detectable levels of endogenous Sigma receptor.

2. (currently amended) The non-human ~~Non-human~~ mutant mammal according to claim 1, wherein said non-human mutant mammal is a heterozygous mutant for said mutation.

3. (currently amended) The non-human ~~Non-human~~ mutant mammal according to claim 1, wherein said non-human mutant mammal is a homozygous mutant for said mutation.

4. (currently amended) The non-human ~~Non-human~~ mutant mammal according to claim 1, wherein said non-human mammal is a mouse.

5. (currently amended) The non-human ~~Non-human~~ mutant mammal according to claim 1, wherein the genome of the non-human mutant mammal comprises a transgene within the mutation introduced in the endogenous Sigma-1 receptor gene that comprises a gene encoding a positive selection marker.

6. (currently amended) The non-human ~~Non-human~~ mutant mammal according to claim 5, wherein said transgene comprises the neomycin phototransferase (*neo*) gene.

7. (currently amended) The non-human ~~Non-human~~ mutant mammal according to claim 1, wherein said Sigma receptor is selected from the group consisting of ~~among~~ a type 1 Sigma receptor (Sigma-1) and a type 2 Sigma receptor (Sigma-2).

8. (currently amended) The non-human ~~Non-human~~ mutant mammal according to claim 1, wherein said non-human mutant mammal is a mutant mouse, deficient in the endogenous Sigma-1 receptor, homozygous for the mouse Sigma-1 receptor gene, fertile, whose genome contains a disruption in said gene comprising the *neo* gene.

9. (currently amended) A homologous recombination vector with positive-negative selection, comprising:

a ~~A~~ first homology region positioned at the 5' end of a nucleotide sequence encoding a positive selection marker, wherein said first homology region has a nucleotide sequence that is substantially identical to a first sequence of a Sigma receptor gene;

a ~~A~~ nucleotide sequence encoding a positive selection marker;

a ~~A~~ second homology region positioned at the 3' end of said nucleotide sequence encoding a positive selection marker, wherein said second homology region has a nucleotide sequence that is substantially identical to a second nucleotide sequence of said Sigma receptor gene, this second sequence of the Sigma receptor gene being positioned at 3' to the first sequence of the Sigma receptor gene in a wild type endogenous Sigma gene; and

a ~~A~~ nucleotide sequence encoding a negative selection marker.

10. (currently amended) The ~~A~~ vector according to claim 9, wherein said Sigma receptor gene is selected from the group consisting of a ~~among the~~ type 1 Sigma receptor gene (Sigma-1) and a ~~the~~ type 2 Sigma receptor gene (Sigma-2).

11. (currently amended) A vector according to claim 9, wherein said second nucleotide sequence encoding a positive selection marker comprises a ~~the~~ neomycin phototransferase (*neo*) gene.

12. (currently amended) The ~~A~~ vector according to claim 9, wherein said nucleotide sequence encoding a positive selection marker comprises a ~~the~~ thymidin kinase (*tk*) gene of the herpes simplex virus (HSV).

13. (currently amended) The ~~A~~ vector according to claim 9, identified as pHR53TK, deposited in Spanish Type Culture Collection (CECT) of the University of Valencia with access number CECT 5737.

14. (currently amended) A host cell whose genome comprises ~~contains~~ an endogenous Sigma receptor gene transfected with a homologous recombination vector with positive-negative selection according to claim 9 ~~any of claims 9 to 13~~, deficient in an endogenous Sigma receptor.

15. (currently amended) The ~~A~~ cell according to claim 14, wherein said host cell whose genome contains an endogenous Sigma receptor gene is selected from the group consisting of ~~among~~ a differentiated cell that normally expresses the product of the Sigma receptor gene and a pluripotent embryonic cell.

16. (currently amended) The ~~A~~ cell according to claim 14, comprising an allele of the mutated Sigma-1 receptor gene.

17. (currently amended) An isolated cell from a non-human mutant mammal, deficient in an endgenous Sigma receptor, according to claim 1 ~~any of claims 1 to 8~~, or its offspring.

18. (currently amended) The ~~A~~ cell according to claim 17, comprising one or both mutated alleles of the Sigma receptor gene.

19. (currently amended) The ~~A~~ cell according to claim 17 ~~any of claims 17 or 18~~, wherein the cell is propagated ~~and optionally immortalised~~.

20. (currently amended) The offspring of a non-human mutant mammal deficient in an endogenous Sigma receptor, according to claim 1 ~~any of claims 1 to 8~~.

21. (currently amended) A process for making a non-human mutant mammal according to claim 1 ~~according to any of claims 1 to 8~~, comprising:

introducing ~~the introduction of~~ a functional disruption in an endogenous Sigma receptor gene present in a cell genome by homologous recombination in said cell between an allele of an endogenous Sigma receptor gene and a homologous recombination vector with positive-negative selection according to claim 9 ~~any of claims 9 to 13~~,

selecting ~~the selection of~~ the recombinant homologues by the positive-negative selection technique,

introducing ~~the introduction of~~ said recombinant homologues in embryos,

implanting said embryos ~~their implantation in~~ receptor pseudogestating female mammals,

carrying, by the female mammals, the embryos ~~and their carriage~~ to term,

selecting ~~selection of the~~ chimeras able to efficiently transmit the genotype of the recombinant homologues to their offspring by the germ line, and

crossing said chimeras with non-human wild-type mammals to obtain heterozygous mutants to disrupt the endogenous Sigma receptor.

~~and, if desired, crossing of said heterozygous mutants with each other to obtain homozygous mutants.~~

22. (currently amended) A method for utilizing ~~Use of~~ a non-human mutant mammal according to claim 1, comprising: ~~any of claims 1 to 8 as~~

providing the mammal as a control animal; and ~~animals~~

conducting ~~to conduct~~ *in vivo* tests utilizing the mammal.

23. (currently amended) A method for utilizing ~~Use of~~ a non-human mutant mammal deficient in the Sigma-1 receptor, or of a cell line deficient in the Sigma-1 receptor, comprising:

evaluating ~~to evaluate~~ potentially useful compounds designed ~~meant~~ to perform at least one of the following functions:

at least one of preventing or treating ~~prevent and/or treat~~ disorders of the central nervous system;

at least one of preventing or treating ~~prevent and/or treat~~ memory alterations;

at least one of preventing or treating ~~prevent and/or treat~~ stress conditions;

at least one of preventing or treating ~~prevent and/or treat~~ drug addiction conditions;

producing ~~produce~~ analgesia; and ~~or~~

producing ~~produce~~ neuroprotection.

24. (currently amended) A method for utilizing ~~Use of~~ a non-human mammal deficient in the Sigma-2 receptor, or of a cell line deficient in the Sigma-2 receptor, in a method comprising:

utilizing the mammal for at least one of the following functions:

at least one of validating and developing ~~validation and/or development of~~ drugs designed for diagnosis or treatment of cancer,

at least one of preventing and treating ~~prevention and/or treatment of~~ degenerative processes, and ~~or~~

at least one of preventing, reducing, and alleviating ~~to prevent, reduce or alleviate the~~ side effects associated with an ~~the~~ administration of neuroleptic agents.

25. (currently amended) A method for determining an ~~the~~ effect of a compound to be tested on a non-human mammal deficient in an endogenous Sigma receptor, comprising: ~~which comprises~~

placing in contact a non-human mutant mammal according to claim 1 ~~any of claims 1 to 8~~ with said compound, and

detecting a ~~the~~ presence or absence of a physiological change in said non-human mutant mammal in response to the contact with said compound.

26. (currently amended) A method for determining an ~~the~~ effect of a compound to be tested on a non-human mammal deficient in an endogenous Sigma receptor, comprising: ~~which comprises~~

administering said compound to be tested to a non-human mutant mammal according to claim 1 ~~any of claims 1 to 8~~;

administering said compound to be tested to a control non-human mammal expressing a functional endogenous Sigma receptor; and

observing if said compound has an effect on a ~~the~~ phenotype of said non-human mutant mammal when compared to the control non-human mammal.

27. (currently amended) A method for determining an ~~the~~ effect of a compound on cells expressing a Sigma receptor and on cells not expressing said Sigma receptor, comprising: ~~which comprises~~

introducing a compound to be tested in a cell population or in a homogenisation thereof, wherein said cells are isolated established cells from a non-human mutant mammal according to claim 1 ~~any of claims 1 to 8~~,

administering said compound to be tested to a population of ~~the~~ control non-human mammal cells or to a homogenisation thereof, which expresses a functional Sigma receptor, and

observing or analysing whether said compound to be tested has an effect on the expression of said Sigma receptor in the cells of said non-human mutant mammal when compared to the cells of a control non-human mammal.

28. (new) The cell according to claim 19 wherein the cell is immortalized.

29. (new) The process according to claim 21, further comprising:

crossing said heterozygous mutants with each other to obtain homozygous mutants.